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NONPEPTIDE GLYCOPROTEIN IIb/IIIa INHIBITORS: SUBSTITUTED QUINAZOLINEDIONES AND QUINAZOLINONES AS POTENT FIBRINOGEN RECEPTOR ANTAGONISTS

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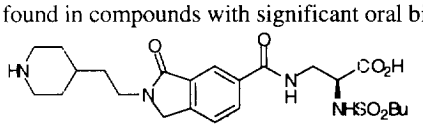
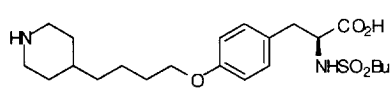
Abstract: The synthesis and biological activity of a series of 3,6-substituted quinazolinediones and quinazolinones are described. The potent activity of these compounds as platelet aggregation inhibitors demonstrates the utility of these structures as central templates for nonpeptide RGD mimics.

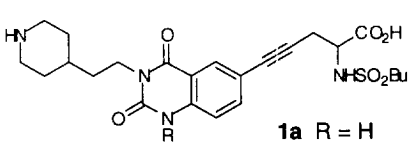
The activation and aggregation of platelets to form arterial thrombi can lead to a number of disease states including unstable angina, myocardial infarction, and arterial reocclusion following angioplasty.[1,2] By preventing platelet aggregation at a common step in the clotting cascade, fibrinogen receptor antagonists may offer advantages over other classes of drugs that exert effects on specific activation pathways.[3,4] A number of RGD containing peptides including echistatin[5] and the cyclic peptide MK0852[6] inhibit platelet aggregation. Recent work in these laboratories resulted in the identification of the tyrosine derivative (Aggrastat®, L-700,462),[7] a potent nonpeptide RGD mimic. As a short acting iv platelet aggregation inhibitor, compounds such as Aggrastat® may prove useful in an acute setting where the effect can be rapidly terminated, if for example surgical intervention becomes necessary. For the chronic management of untoward thrombosis, orally active compounds that have a longer duration of action would be required. One hypothesis was that compounds with constrained central frameworks in place of the tyrosine unit of (Aggrastat® L-700,462) or the benzolactam of L-732,821[8] would enhance bioavailability and improve duration. In this paper we report the use of 3,6-substituted quinazolinediones or quinazolinones as the core templates to give compounds such as **1** and **2**. Both of these structural elements can be found in compounds with significant oral bioavailability.[9]



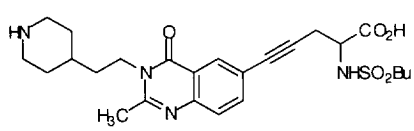
L-732,821



MK383



1a R = H
1b R = Me
1c R = $PhCH_2$
1d R = 4-pyridylCH_2



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0960-894X/98/$19.00
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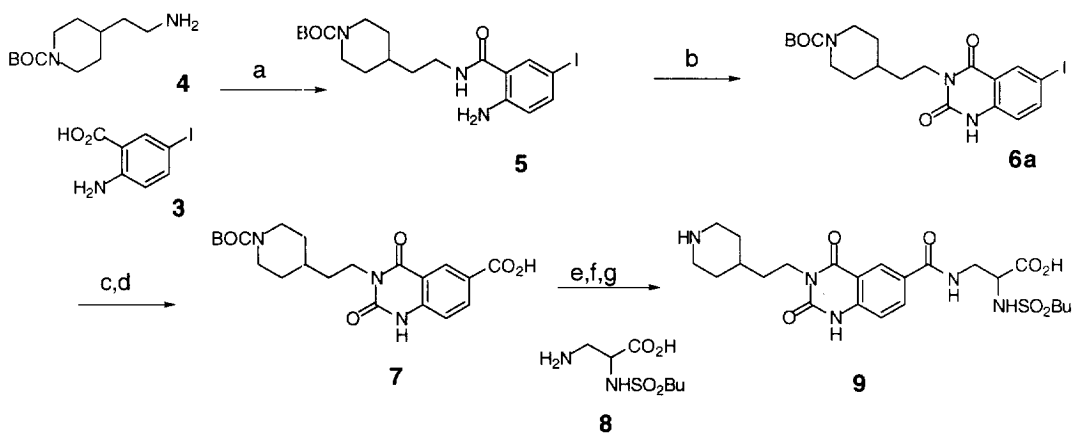
Synthesis:[10]

The quinazolinedione series of compounds was prepared as shown in Scheme 1. EDC coupling of 2-amino-5-iodobenzoic acid **3** with 4-(2-aminoethyl)piperidine **4**[11] gave amide **5**. Cyclization was effected by treatment with carbonyldiimidazole in THF at 60 °C to give the key intermediate, iodoquinazolinedione **6a**. The corresponding benzoic acid **7** was obtained by the palladium catalyzed tributyltin hydride carbonylation of iodide **6a** under 1 atmosphere of carbon monoxide,[12] followed by sodium chlorite/hydrogen peroxide oxidation[13] in 85% overall yield. EDC coupling with 2-(1-butanesulfonamido)-β-alanine **8**[14] and deprotection of the carboxyl and amino groups afforded **9**.[15] Preparation of carboxyl terminus analogs in which the amide linkage is replaced by an acetylene or ethylene group was achieved by palladium catalyzed coupling[16] of ethyl 2-(1-butanesulfonamido)pent-4-yn-1-oate **10**[17] with iodide **6a**, affording acetylene **11a** (Scheme 2). Deprotection afforded the final product **1a** and the corresponding saturated derivative **12a** was obtained by catalytic hydrogenation of **11a** followed by deprotection.

Scheme 1

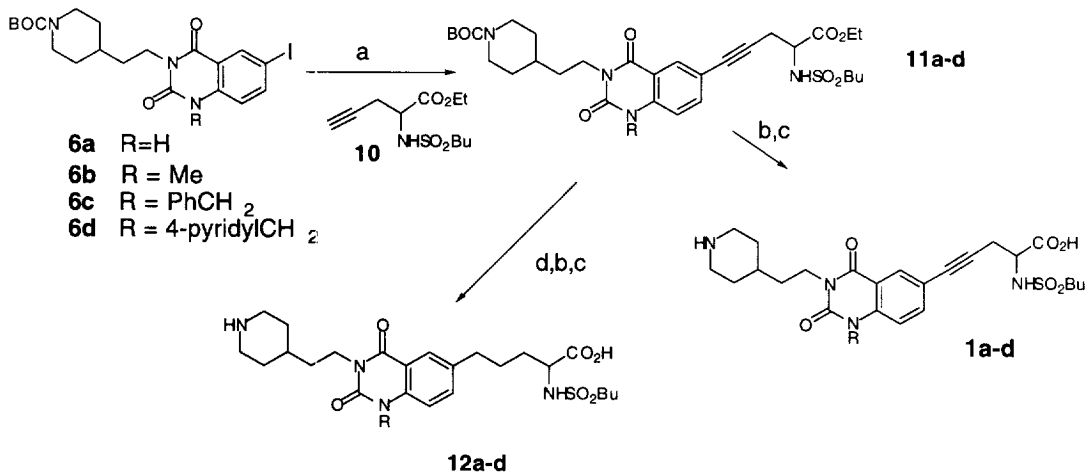


(a) EDC, HOBt, NEt_3, DMF, rt, 56%; (b) carbonyldiimidazole, THF, 60 °C, 3 h, 70%; (c) $Pd(PPh_3)_4$, CO (balloon), toluene, slow addition of Bu_3SnH, 50 °C; (d) H_2O_2, $NaClO_2$, Phosphate buffer pH 4.3, rt; (e) **8**, EDC, HOBt, NEt_3, DMF, rt; (f) LiOH, THF, H_2O; (g) HCl, EtOAc, 0 °C.

The effect of substitution at N-1 was investigated by alkylation of iodoquinazolinedione **6a** with either methyl iodide or benzyl bromide and potassium hydride in THF, or 4-chloromethylpyridine and potassium carbonate in acetonitrile. The corresponding alkylated compounds **6b–d** were converted to acetylenes **1b–d** in the same manner described for **1a** and the corresponding saturated derivatives **12b–d**.

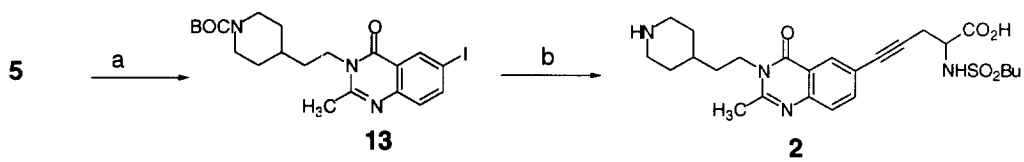
Cyclization of amide **5** by treatment with triethyl orthoacetate at 160 °C afforded the quinazolinone intermediate **13** (Scheme 3). This was coupled with acetylene **9** and deprotected in the same way as in the quinazolinedione series to give the quinazolinone **2**

Scheme 2



(a) **10**, $Pd(PPh_3)_4$, CuI, $HNEt_2$, 40 °C (b) LiOH, THF, H_2O (c) HCl, EtOAc, 0 °C (d) H_2, 50psi, Pd/C, EtOAc

Scheme 3



(a) $(EtO)_3CH$,160 °C, 3 h, 93%; (b) steps a,b,c from Scheme 2

Biological Activity

The compounds were evaluated as platelet aggregation inhibitors by measuring their effect on the ADP stimulated aggregation of human platelets in vitro [5] and the data are shown in Table 1. While the β-alanine analog **9** was considerably less potent than benzolactam L-732,821, replacement of the C-terminal amide linkage with an acetylene to give **1a**, improved activity considerably suggesting that the amide is not involved in any hydrogen bonding interactions with the receptor. Good in vitro activity was maintained for a range of substitution on N1, as demonstrated by **1b**, **1c,** and **1d**, suggesting that this part of the molecule is not in close contact with the receptor and probably corresponds to the interior of cyclic RGD containing peptides. As this observation would suggest, the quinazolinone derivative **2**, which presents the amine and carboxyl termini in the same manner, shows essentially identical activity to the corresponding quinazolinedione **1a**. Reduction of the acetylene to give the saturated compounds **12a–d** consistently caused only a slight decrease in activity, less than might be expected as a consequence of the significant change in geometry and increase in the conformational flexibility of the carboxyl containing side chain. As has been suggested previously,[18] the central restraint appears to function largely as a scaffold providing appropriate positioning for the carboxyl, amino and "exosite"[7] sulfonamide binding elements and allows for considerable structural diversity. The structural and substituent tolerance of the central restraints

described here suggests that appropriate modification of this portion of RGD mimetics may provide a means to altering pharmacokinetic parameters while maintaining good in vitro potency.

These compounds were found to have a relatively short duration of action following iv infusion in dogs and as a result, their oral bioavailability was not determined.

Table 1

Compound	Platelet Aggregation $IC_{50}(\mu M)$
L-732,821	0.009
Aggrastat®	0.015
9	0.21
1a	0.037
1b	0.067
1c	0.061
1d	0.074
12a	0.16
12b	0.14
12c	0.16
12d	0.10
2	0.043

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